Sepsis phenotypes, subphenotypes, and endotypes: are they ready for bedside care?

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Purpose of review
Sepsis remains a leading global cause of morbidity and mortality, and despite decades of research, no effective therapies have emerged. The lack of progress in sepsis outcomes is related in part to the significant heterogeneity of sepsis populations. This review seeks to highlight recent literature regarding sepsis phenotypes and the potential for further research and therapeutic intervention.

Recent findings
Numerous recent studies have elucidated various phenotypes, subphenotypes, and endotypes in sepsis. Clinical parameters including vital sign trajectories and microbial factors, biomarker investigation, and genomic, transcriptomic, proteomic, and metabolomic studies have illustrated numerous differences in sepsis populations with implications for prediction, diagnosis, treatment, and prognosis of sepsis.

Summary
Sepsis therapies including care bundles, fluid resuscitation, and source control procedures may be better guided by validated phenotypes than universal application. Novel biomarkers may improve upon the sensitivity and specificity of existing markers and identify complications and sequelae of sepsis. Multiomics have demonstrated significant differences in sepsis populations, most notably expanding our understanding of immunosuppressed sepsis phenotypes. Despite progress, these findings may be limited by modest reproducibility and logistical barriers to clinical implementation. Further studies may translate recent findings into bedside care.

Keywords
biomarker, endotype, heterogeneity, multiomics, phenotype, sepsis

INTRODUCTION

In 2017, the World Health Assembly, the decision-making body of the World Health Organization, adopted a resolution to improve the prevention, diagnosis, and management of sepsis, highlighting sepsis as a global health priority [1]. Sepsis is currently defined as life-threatening organ dysfunction resulting from infection [2]. Though previous studies estimated an annual incidence of 31.5 million sepsis episodes and 5.3 million sepsis deaths [3], data for low- and middle-income countries are lacking. More recent estimates including these data suggest a staggering 48.9 million incident cases of sepsis and 11.0 million sepsis-related deaths annually, accounting for nearly 20% of all global deaths. Despite decades of research involving tens of thousands of patients and hundreds of millions of dollars [4], no effective therapies have emerged to definitely improve patient outcomes [5]. The notable lack of progress in sepsis research and therapy is likely multifactorial, including inherent pathophysiologic complexity [6] and inadequate conceptual models [7,8]. However, the significant heterogeneity in sepsis populations likely also contributes. In recent years, there has been significant interest in better stratifying sepsis populations to improve research, trial design, and clinical outcomes [9]. Historical stratification of sepsis populations relied on clinical definitions to better identify heterogeneity, but novel approaches to characterize sepsis include genetic, metabolic, and immunologic parameters to identify populations and sub-populations that may benefit from therapeutic intervention [10]. This

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KEY POINTS

- The lack of progress in sepsis outcomes is multifactorial and may relate to the heterogeneity of sepsis populations.
- Phenotypes are a set of clinical features in patients with a common condition, subphenotypes are a set of features in patients who share a phenotype, and endotypes are unique biological mechanisms of disease shared by a subgroup of patients.
- Numerous phenotypes, subphenotypes, and endotypes of sepsis have been described in recent literature based on clinical and molecular evaluation.
- Multiomics elucidate the biochemical and molecular mechanisms of sepsis and provide a foundation for personalized and precision medicine.
- Prospective trials of sepsis phenotypes and endotypes may identify therapeutic targets.

review highlights recent literature regarding phenotypes, subphenotypes and endotypes of sepsis and discusses their implications for clinical application.

REVIEW

Clinical parameters

Though historically imprecise, recent research has shown progress in the clinical stratification of sepsis. A classification of 120 patients with septic shock and 88 patients with *S. aureus* bacteremia into previously validated temperature subphenotypes found significant associations between temperature trajectory and inflammatory cytokines between the two cohorts [11]. Hypothermic patients had the lowest levels of most pro- and anti-inflammatory cytokines compared to hyperthermic patients, with a trend toward higher mortality. A retrospective analysis of 20 729 patients with suspected infection stratified into four vital sign trajectory subphenotypes found significantly higher 30-day mortality in Group A (hyperthermic, tachycardic, tachypneic, and hypotensive) and Group D (lower temperatures, heart rates, and respiratory rates, hypotensive) patients [12]. In addition, groups differed based on laboratory parameters, organ dysfunction patterns, and response to fluid resuscitation. These results suggest that universally available vital sign trajectories may reflect molecular correlates and could have both prognostic and therapeutic implications.

Though sepsis mortality has improved in recent decades, this is largely attributable to bundle protocols involving early identification, diagnostic evaluation, and administration of timely antimicrobials and resuscitative fluids in sepsis patients. Recent studies have called into question the utility of universal care bundles for sepsis patients. An observational study of 55 169 adult hospitalizations with community-acquired sepsis stratified into four sepsis subtypes found an association between time to treatment and outcome, which was modified by clinical sepsis subtype [13▪]. Each hour of time to completion of the 3-h bundle and initiation of antibiotics associated with increased risk of in-hospital mortality, whereas time to intravenous fluid bolus completion was not associated with in-hospital mortality. A retrospective analysis of 320 sepsis patients found significant differences in in-hospital mortality among clinical sepsis phenotypes, with a trend toward positive volume balance in nonsurvivor versus survivor groups [14]. A large Bayesian analysis of randomized controlled trials (RCTs) showed significant increase in mortality with bundled fluid resuscitation in patients with elevated APACHE II score [15]. These data suggest that sepsis therapeutic intervention – particularly fluid resuscitation – may be more safely directed by patient subtype than general application.

Aside from host features, clinical stratification based on pathogen factors may help differentiate patients with sepsis. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) evaluated 343 million individual records or isolates across 204 countries and estimated that 33 bacterial pathogens accounted for 13.6% of all global deaths and 56.2% of all sepsis-related deaths in 2019 alone [16]. Of the 33 pathogens, five (*S. aureus*, *E. coli*, *S. pneumoniae*, *K. pneumoniae*, and *P. aeruginosa*) accounted for nearly 55% of deaths. Antimicrobial resistance among bacterial isolates may also play a role, with an estimated 4.95 million deaths associated with antimicrobial resistance in 2019 [17].

Anatomic source of infection is another factor of interest in sepsis. Leligdowicz *et al.* retrospectively evaluated 7974 patients with septic shock across 29 academic and community intensive care units (ICUs) and found a statistically significant mortality difference with anatomic source of infection; hospital mortality was highest for those with intra-abdominal infection from ischemic bowel and disseminated infections and lowest for those with urinary tract infections from obstructive uropathy [18]. A retrospective study by Jeganathan *et al.* also found a significant difference in patient mortality based on source of sepsis [19]. Additionally, source control within 6 h of sepsis onset was associated with a 29% reduction in risk-adjusted odds of 90-day mortality in a cohort of hospitalized adults with sepsis [20], and a secondary analysis of 1077 adult ICU patients with secondary peritonitis found that emergency

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(<2 h) and delayed (>6 h) source control was associated with worse clinical outcomes compared with an urgent (2–6 h) surgical approach [21].

In summary, these studies highlight clinical factors of both host and pathogen that may help identify subpopulations of sepsis and suggest differences in response to therapy and prognosis.

Biomarkers

Biomarkers have long been utilized as a method of identifying and differentiating patients with sepsis. Although theoretically useful in differentiating bacterial versus nonbacterial infections, numerous meta-analyses of procalcitonin (PCT) for diagnosis of sepsis showed a sensitivity range of only 77–85% and a specificity range of 75–83% [22▪▪]. Similarly, a recent retrospective observational cohort study of 74 958 adult patients in whom blood cultures and PCT were obtained demonstrated poor to moderate discrimination of bacteremic sepsis and bloodstream infection for PCT [23]. However, other studies suggest possible utility in PCT testing. A retrospective observational study including 194 children <14 years with sepsis, septic shock, and bacterial meningitis found a PCT level >19 ng/ml on arrival was significantly associated with higher risk of short- and long-term complications, need for PICU, and mortality [24]. Additionally, increase in PCT 24 h after admission associated with higher risk of long-term sequelae and mortality.

C-reactive protein (CRP) has potential utility in prediction of sepsis but has a sensitivity range of 78–80% and specificity range of 60–61% for diagnosis of sepsis [22▪▪]. However, CRP may have value in prognostication and phenotype stratification. A systematic review and meta-analysis including 3224 patients with sepsis found the ratio of CRP to albumin (CAR) was associated with increased mortality and poor prognosis [25]. A multicenter cohort study of 483 adult patients who survived hospitalization for sepsis found the hyperinflammation phenotype – characterized by high levels of interleukin (IL)-6 and CRP – had higher 1-year mortality [26].

Novel biomarkers have also been evaluated. A systematic review and meta-analysis of biomarkers for diagnostic accuracy in adult sepsis including 22 459 patients showed monocyte distribution width (MDW) had significantly higher pooled sensitivity but significantly lower pooled specificity compared to procalcitonin, with similar pooled sensitivity and specificity compared to CRP [27]. Presepsin is a subtype of soluble CD14, which acts as a receptor for lipopolysaccharide (LPS) and contributes to activation of the inflammatory cascade. Presepsin has shown high sensitivity and good specificity for diagnosing sepsis in some studies, though other reports suggest utility only as an adjunct to other biomarkers [28]. A biomarker panel in 23 trauma patients and 23 sepsis patients found that a combination of biomarkers – including TREM1, IL1F10, Serpin A9, A2M, GPI – may differentiate septic patients from those with trauma-induced sterile inflammation [29▪].

Coagulopathy is a common complication of sepsis, and biomarkers may have a role in the diagnosis and prognosis of sepsis-induced coagulopathy (SIC). Potential biomarkers of SIC include soluble thrombomodulin (sTM), thrombin–antithrombin complex (TAT), tissue plasminogen activator–inhibitor complex (t-PAIC), and α2-plasmin inhibitor-plasmin complex (PIC). A prospective observational study including 444 patients with disseminated intravascular coagulation (DIC) showed the combination of these markers provided reliability in predicting DIC, and several showed prognostic value in predicting poor outcomes [30]. A prospective study involving 82 patients with sepsis suggested increased neutrophil extracellular trap (NET) formation was significantly associated with DIC incidence and mortality in sepsis patients [31]. Higher plasma levels of tissue inhibitor of metalloproteinase-1 (TIMP-1) were associated with shock, acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and mortality in a prospective study of 334 patients with sepsis, and matrix metalloproteinase-3 (MMP) associated with shock and mortality [32]. These and other biomarkers may help in the prediction and diagnosis of sepsis, including identification of complications and comorbid conditions.

Multiomics

Much of the recent literature dedicated to understanding sepsis and sepsis populations has involved the study of various biologic signals, including genomics, transcriptomics, proteomics, and metabolomics, collectively referred to as "multiomics" [33▪▪]. Although largely still a developing field, multiomics represent precise molecular tools to advance understanding of the pathophysiologic mechanisms of sepsis and improve identification, treatment, and prognostication of sepsis.

A prospective observational cohort study of blood gene expression profiles in 306 sepsis patients found four molecular endotypes, termed Mars1–4 [34]. The Mars1 endotype was characterized by significantly higher mortality compared to all other endotypes and a decrease in gene expression corresponding to innate and adaptive immune functions including toll-like receptor (TLR), nuclear factor κβ (NFκβ1) signaling, antigen presentation, and T-cell

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receptor signaling. Furthermore, the authors report that biomarkers were derived for each endotype, facilitating future clinical application.

A recent genomic study identified another immunocompromised disease endotype in sepsis characterized by expanded populations of immature neutrophils, suppression of $CD4^+$ T cells, and alterations in granulopoiesis [35]. Additionally, this endotype was seen across multiple infectious etiologies and syndromes and associated with worse outcomes. Murine models of sepsis also support the importance of intact granulopoiesis; neonatal mice deficient in soluble endogenous protein developmental endothelial locus (DEL-1), essential for promoting emergency granulopoiesis, displayed neutropenia, impaired clearance of bacteremia, and increased mortality which were ameliorated by exogenous DEL-1 administration [36]. Genomic therapy has further elucidated the cellular death mechanisms of sepsis. Pyroptosis is an inflammatory form of cell death involved in pathogen elimination and immune activation. A study estimating expression levels of pyroptosis-related genes (PRG) in patients with sepsis and healthy volunteers used a risk prediction model to effectively predict the risk of sepsis and identify two distinct subtypes of sepsis based on PRG clusters [37]. These studies suggest possible therapeutic benefit in reconstituting beneficial immune responses in sepsis.

Metagenomic next-generation sequencing (mNGS) is at the forefront of genomic study in sepsis. This technology provides quantitative or semiquantitative data regarding concentration of organisms, enabling the ability to detect fastidious or unexpected pathogens and provide an etiologic diagnosis. Prospective samples from blood and bronchoalveolar lavage fluid (BALF) from 50 patients with sepsis found higher detection rates with mNGS compared to blood and BALF culture, with increased detection of numerous bacteria, fungi and viruses [38]. In a systematic review and meta-analysis of mNGS to evaluate sepsis etiology, Li *et al.* found a pooled sensitivity of 0.89 and pooled specificity of 0.40 [39▪]. The utility of testing in immunocompromised patients is of special importance. A study evaluating 308 patients with sepsis found a higher sensitivity of mNGS compared to culture methods, with considerably more sensitivity in the immunocompromised group [40]. Additionally, mNGS resulted in a positive or neutral effect in 235 (76.3%) patients, including detection of more pathogens and assurance for antibiotic de-escalation. Thus, genomic studies can also assist in the identification of etiologic pathogens for risk stratification and targeted therapy.

Transcriptomics and proteomics are another area of interest in identifying subpopulations of sepsis. A comparative analysis of targeted plasma proteomics revealed a shared core response to infection between patients with sepsis and coronavirus disease 2019 (COVID-19), with protein signatures in sepsis characterized by relatively elevated proinflammatory cytokines and protein signatures in COVID-19 characterized by markers of tissue damage and wound repair [41]. A transcriptomic score based on expression of 8 genes in critically ill patients with sepsis, trauma, and burns identified a high-risk group differentiated by features of immune suppression including low HLA-DR levels, high immature neutrophil rate, and higher circulating IL-10 values [42]. Compared to the low-risk group, the high-risk group had increased risk of ICU-related infections, longer duration of ICU stay, and higher mortality. Other transcriptomic studies have further elucidated the immune suppression observed in sepsis. An RNA-sequencing analysis of circulating immune cell profiles in septic patients revealed a monocyte subset characterized by high expression of S100A genes and low expression of HLA-DR [43]. A similar monocyte subtype in a murine model of sepsis exhibited suppression of $CD4^+$ T cell function and contributed to an immunosuppressed phenotype. Despite these studies, a recent RCT of 98 patients with sepsis and immune suppression (defined as low mHLA-DR expression) found no significant difference in ICU-acquired infection or 28-day mortality between those receiving and those not receiving GM-CSF [44], highlighting the need for additional studies.

Metabolomics, the utilization of metabolic profiling, may have numerous applications in sepsis including identification of pathogenic etiology, anatomic location of infection, and metabolic perturbations that may portend sepsis severity and prognosis. Clustering of plasma metabolic profiles has revealed 3 distinct clusters of plasma lipids – including fatty acid metabolites, lysophospholipids, and sphingolipids – that associated with high mortality and rates of septic shock [45]. A retrospective study of 84 ARDS patients identified 102 metabolites that differentiated sepsis-induced ARDS from non-ARDS controls, and 14 metabolites that identified direct and indirect ARDS subphenotypes [46]. Multiomics thus represent innovative and precise methods for the evaluation and stratification of sepsis patients.

CONCLUSION

Sepsis remains among the leading global causes of death. Efforts to improve the substantial mortality of sepsis are hampered in part by the heterogeneity of sepsis populations. Despite this, recent literature highlights advancements in our ability to differentiate sepsis populations (summarized in Table 1). Clinical stratification using universally available

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Table 1. Summary of sepsis subpopulation parameters and findings

Parameter	Population/study	Findings	Reference
Temperature trajectory	120 patients with septic shock, 88 patients with *S. aureus* bacteremia	Hypothermic patients had the lowest levels of most pro- and anti-inflammatory cytokines and a trend toward higher mortality	Bhavani SV, Wolfe KS, Hrusch CL, *et al.* [11]
Vital sign trajectory	20 729 patients with suspected infection	Higher 30-day mortality in Group A (hyperthermic, tachycardic, tachypneic and hypotensive) and Group D (lower temperatures, heart rates, and respiratory rates, hypotensive) patients	Bhavani SV, Semler M, Qian ET, *et al.* [12]
SENECA clinical sepsis subtypes: α, β, γ, δ	55 169 adult hospitalizations with community-acquired sepsis	Each hour to completion of a 3-h bundle and initiation of antibiotics associated with increased risk of in-hospital mortality	Yang A, Kennedy JN, Reitz KM, *et al.* [13▪]
Clinical sepsis subtypes: multiple organ failure, respiratory dysfunction, neurologic dysfunction, other	320 sepsis patients	Trend toward positive volume balance in nonsurvivor versus survivor groups	Shald EA, Erdman MJ, Ferreira JA. [14]
Early goal-directed therapy	19 998 patients in random-effects and Bayesian hierarchical analyses	Early goal-directed therapy was associated with increased mortality in patients with high disease severity	Kalil AC, Johnson DW, Lisco SJ, *et al.* [15]
Bacterial species	343 million individual records or isolates	33 pathogens accounted for 13.6% of all global deaths and 56.2% of all sepsis-related deaths in 2019	GBD 2019 Antimicrobial Resistance Collaborators [16]
Bacterial isolates	471 million individual records or isolates	4.95 million deaths associated with bacterial antimicrobial resistance in 2019	GBD 2019 Antimicrobial Resistance Collaborators [17]
Anatomic source of infection	7974 patients with septic shock	Statistically significant mortality difference based on anatomic location of infection	Leligdowicz A, Dodek PM, Norena M, *et al.* [18]
Anatomic source of infection	248 patients with sepsis	Mortality, length of stay, and cost difference based on source of sepsis	Jeganathan N, Yau S, Ahuja N, *et al.* [19]
Procedural source control	4962 patients with sepsis	Source control within 6 h of sepsis onset was associated with a 29% reduction in risk-adjusted odds of 90-day mortality	Reitz KM, Kennedy J, Li SR, *et al.* [20]
Source control intervention	1077 cases of microbiologically confirmed secondary peritonitis	Emergency (<2 h) and delayed (>6 h) source control was associated with worse clinical outcomes compared with urgent (2–6 h) surgical approach	De Pascale G, Antonelli M, Deschepper M, *et al.* [21]
Procalcitonin (PCT)	Three meta-analyses	PCT showed a sensitivity range of 77–85% and specificity range of 75–83% for diagnosis of sepsis	Pvoa P, Coelho L, Dal-Pizzol F, *et al.* [22▪▪]
Procalcitonin (PCT)	74 958 adult patients with concurrent PCT and blood cultures	PCT demonstrated poor sensitivity in ruling out BSI and poor-to-moderate discrimination for bacteremic sepsis and occult BSI	Lawandi A, Oshiro M, Warner S, *et al.* [23]
Procalcitonin (PCT)	194 children <14 years of age with sepsis and bacterial meningitis	PCT level > 19 ng/mL associated with higher risk of short- and long-term complications and mortality; increase in PCT associated with long-term sequelae and mortality	Castagno E, Aguzzi S, Rossi L, *et al.* [24]
C-reactive protein (CRP)	Two meta-analyses	CRP showed a sensitivity range of 78–80% and specificity range of 60–61% for diagnosis of sepsis	Pvoa P, Coelho L, Dal-Pizzol F, *et al.* [22▪▪]
C-reactive protein-to-albumin ratio (CAR)	3224 patients with sepsis	CAR associated with increased mortality and poor prognosis	Liu Y, Gao Y, Liang B, *et al.* [25]

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Table 1 (*Continued*)

Parameter	Population/study	Findings	Reference
Biomarker phenotypes	483 adult patients who survived hospitalization for sepsis	Hyperinflammation (high IL-6 and CRP levels) and immunosuppression (high sPD-L1 levels) phenotypes had higher 1-year mortality rates	Barichello T, Generoso JS, Singer M, *et al.* [26]
Monocyte distribution width (MDW)	22 459 adult patients with sepsis	MDW had significantly higher pooled sensitivity but significantly lower pooled specificity compared to PCT; similar pooled sensitivity and specificity compared to CRP	Huang Y-H, Chen C-J, Shao S-C, *et al.* [27]
Presepsin	100 patients with suspected infection; 70 with sepsis	Presepsin and PCT had similar efficacy in diagnosing sepsis; other studies suggest utility in combination with other biomarkers	Juneja D, Jain N, Singh O, *et al.* [28]
Biomarker panel	23 trauma patients, 23 sepsis patients	A combination of biomarkers may differentiate sepsis from trauma-induced inflammation	Papareddy P, Selle M, Partouche N, *et al.* [29▪]
Coagulation biomarkers	444 patients with DIC, 137 healthy individuals	Coagulation biomarkers showed prognostic value in predicting DIC and predicting poor outcomes	Li Y, Li H, Wang Y, *et al.* [30]
Neutropohil extracellular trap (NET)	82 patients admitted with sepsis	NET formation was significantly associated with DIC incidence and mortality	Mao J-Y, Zhang J-H, Cheng W, *et al.* [31]
Tissue inhibitor of metalloproteinase-1 (TIMP-1) and Matrix metalloproteinase-3 (MMP)	334 patients with sepsis	TIMP-1 associated with shock, ARDS, AKI and mortality; MMP associated with shock and mortality	Jones TK, Reilly JP, Anderson BJ, *et al.* [32]
Multiomics	Review	Review of multiomics to define endotypes in sepsis and septic shock	Garduno A, Cusack R, Leone M, *et al.* [33▪▪]
Gene expression profiles	306 sepsis patients	Four molecular endocytpes (Mars1–4); Mars1 characterized by higher mortality and decrease in innate and adaptive immunity gene expression	Scicluna BP, Van Vught LA, Zwinderman AH, *et al.* [34]
Whole-blood single-cell multiomic atlas	26 patients with all-cause sepsis	Immunocompromised disease endotype characterized by immature neutrophils, suppression of CD4+ T cells and altered granulopoiesis associated with worse outcomes	Kwok AJ, Allcock A, Ferreira RC, *et al.* [35]
Developmental endothelial locus (DEL-1)	Murine model of sepsis	Neonatal mice dificient in DEL-1 displayed neutropenia, impaired bacterial clearance, and increased mortality	Vergadi E, Kolliniati O, Lapi I, *et al.* [36]
Pyroptosis-related genes (PRG)	760 sepsis patients, 42 healthy individuals	Two distinct subtypes of sepsis based on PRG clusters; risk prediction model can effectively predict risk of sepsis	Ding W, Huang L, Wu Y, *et al.* [37]
Metagenomic next-generation sequencing (mNGS)	50 patients with sepsis	Overall pathogen detection rates significantly higher with mNGS compared to blood and BAL fluid culture	Chien J-Y, Yu C-J, Hsueh P-R. [38]
Metagenomic next-generation sequencing (mNGS)	Systematic review and meta-analysis	mNGS had a pooled sensitivity of 0.89 and pooled specificity of 0.40 for diagnosis of sepsis	Li D, Yang Y, Xie Y, *et al.* [39▪]
Metagenomic next-generation sequencing (mNGS)	308 total patients with sepsis; 92 immunocompromised	mNGS for pathogen detection had overall sensitivity of 88.0%; sensitivity 91.3% in immunocompromised group	Li X, Liang S, Zhang D, *et al.* [40]
Plasma proteins	Plasma samples from patients with SARS-CoV-2, sepsis, healthy volunteers	Shared core response to infection in COVID-19 and sepsis; higher proinflammatory cytokines in sepsis and markers of tissue damage and wound repair in COVID-19	Palma Medina LM, Babačić H, Dzidic M, *et al.* [41]

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Table 1 (*Continued*)

Parameter	Population/study	Findings	Reference
Transcriptomic score	Gene expression data set from 176 critically ill patients with sepsis, trauma, burns	High-risk patients with increased mortality exhibited features of immune suppression with low HLA-DR, higher immature neutrophil rates, and higher IL-10 levels	Bodinier M, Monneret G, Casimir M, *et al.* [42]
RNA-sequencing analysis	65 septic patients, 19 healthy individuals	Monocyte subset characterized by high expression of S100A genes and low expression of HLA-DR	Yao R-Q, Zhao P-Y, Li Z-X, *et al.* [43]
mHLA-DR	RCT of 98 patients with sepsis-induced immunosuppression (mHLA-DR <8000 ABC)	No significant difference in ICU-acquired infection or 28-day mortality observed between patients randomized to receive GM-CSF or placebo	Vacheron C-H, Lepape A, Venet F, *et al.* [44]
Plasma lipids	197 patients with early sepsis	Three distinct metabolic clusters based on plasma lipids with differing rates of mortality and sepsis shock	Hussain H, Vutipongsatorn K, Jiménez B, *et al.* [45]
Metabolite concentrations	54 samples of ARDS patients and 30 non-ARDS controls	102 metabolites differentiated sepsis-induced ARDS from non-ARDS controls; 14 metabolites identified direct and indirect ARDS subphenotypes	Chang Y, Yoo HJ, Kim SJ, *et al.* [46]
Six sepsis cohorts	63, 547 sepsis patients	Cluster analysis of sepsis cohorts showed modest reproducibility	Zhang Z, Chen L, Liu X, *et al.* [47]

ABC, antibodies bound per cell; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CAR, C-reactive protein-to-albumin ratio; CRP, C-reactive protein; DEL-1, developmental endothelial locus; DIC, disseminated intravascular coagulation; MDW, monocyte distribution width; mHLA-DR, monocytic human leukocyte antigen-DR; MMP, matrix metalloproteinase-3; mNGS, metagenomic next-generation sequencing; NET, neutrophil extracellular trap; PCT, procalcitonin; PRG, pyroptosis-related genes; RNA, ribonucleic acid; TIMP-1, tissue inhibitor of metalloproteinase-1.

vital sign trajectories and microbial factors has identified various sepsis phenotypes. Biomarker investigation has elucidated associations among existing molecules and identified novel markers for clinical use. Multiomics represent a significant advancement in the quest for personalized and precision medicine and offer additional insight into the host immune response to sepsis. Notwithstanding this progress, much work remains. Defining the accurate association between molecular markers and clinical parameters will further assist providers in the clinical care of patients with sepsis. Biomarker and multiomics studies require rigorous validation in high-quality prospective trials and face significant logistical barriers to implementation, including availability, cost, and turnaround time.

We must also display skepticism and temperance when interpreting these studies. A recent evaluation of 6 international sepsis cohorts including 63 547 sepsis patients found only moderate reproducibility [47], and studies attempting to cluster and stratify sepsis populations may suffer from data noise and lack of biological plausibility [48]. Of additional concern is the possibility of spurious correlations, magnified by the large number of participants and variables in many of the sepsis phenotype studies [49,50].

In summary, identification of a more homogenous patient population through phenotypes, subphenotypes, and endotypes may lead to better understanding of sepsis pathophysiology and targets for therapeutic intervention to achieve the ultimate goal of improving the survival of millions of patients affected by sepsis annually.

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Conflicts of interest

There are no conflicts of interest.

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